J Infect Chemother xxx (2017) 1–4

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Importance of vancomycin loading doses in intermittent infusion regimens

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ARTICLE INFO

Article history:
Received 18 May 2017
Received in revised form
11 September 2017
Accepted 1 November 2017
Available online xxx

Keywords:
Vancomycin
Pharmacokinetics
Therapeutic drug monitoring
Loading dose
Intermittent infusion

ABSTRACT

Purpose: Delayed achievement of target vancomycin serum concentrations may adversely affect clinical outcomes. The objective of this retrospective study was to explore the real frequency of loading dose use and to evaluate the impact of loading dose for the achievement of vancomycin PK/PD target in adult patients treated with intermittent vancomycin. As a secondary aim we determined optimal vancomycin loading dose based on individual pharmacokinetic calculations.

Methods: Vancomycin pharmacokinetic models were computed using two-compartmental analysis. Based on these models AUC_{24} were calculated. Unpaired *t*-test was used to compare AUC_{24} achieved in patients treated with and without vancomycin loading dose.

Results: Vancomycin loading dose was administered only in 17.8% patients. Volume of distribution and clearance median values (interquartile range) for vancomycin in whole study population (n = 45) were 0.69 (0.55–0.87) L/kg and 0.0304 (0.0217–0.0501) L/h/kg, respectively. The AUC_{24} was significantly higher in patients taking loading dose compared with the group without loading dose: mean (SD) AUC_{24} was 496 (101) vs. 341 (77) mg h/L. Proportion of patients reaching PK/PD goal was 87.5% and 24.3% with and without loading dose administration, respectively. Considering individual pharmacokinetic parameters optimal vancomycin loading dose was 27.5 mg/kg of body weight.

Conclusions: Loading dose administration plays crucial part in rapid attainment of vancomycin PK/PD target in adult patient treated with intermittent vancomycin, although it is not frequently used in clinical practise. The optimal loading dose of 25–30 mg/kg of body weight should be routinely administered to adult patients treated with intermittent vancomycin.

1. Introduction

Vancomycin, a glycopeptide antibiotic, is one of the first choices for treating serious, nosocomial infections caused by Gram-positive bacteria involving methicillin-resistant *Staphylococcus aureus* [1]. Vancomycin exhibits time-dependent bactericidal activity against sensitive bacteria, while the ratio of the 24-hour area under the concentration-time curve (AUC_{24}) to the minimal inhibitory concentration (MIC) is considered the most adequate pharmacokinetic/pharmacodynamics (PK/PD) parameter to predict clinical and bacteriological outcomes of vancomycin treatment [2]. Based on *in vitro* and limited *in vivo* data, the AUC/MIC ratio of ≥400 mg h/L is recommended as the PK/PD target value for vancomycin by therapeutic guidelines [3]. A recent systematic review and meta-analysis of data published in nine cohort studies by Men et al. has confirmed that the AUC_{24}/MIC ratio of approximately 400 mg h/L results in significantly reduced risk of treatment failure and crude mortality [4].

In case of serious infections, antibiotics should be administered as soon as possible once infection is identified [5,6] and an early attainment of efficacious vancomycin concentrations is crucial for the treatment success [7]. In order to achieve therapeutic serum concentrations as early as possible a loading dose (LD) administration should be considered [8,9].

Consensus review from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the

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https://doi.org/10.1016/j.jiac.2017.11.002
1341-321X/

Society of Infectious Diseases Pharmacists suggested a LD of 25–30 mg/kg of actual body weight to facilitate rapid attainment of target through serum vancomycin concentration in seriously ill patients [1]. However, this recommendation has low level of evidence (III – evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees). In addition, the currently valid summary of product characteristics does not recommend LD administration. This is probably the reason that LD administration is not common in real clinical use.

The aim of our study was to explore the real frequency of LD use and to evaluate the impact of LD for the achievement of vancomycin PK/PD target ($AUC_{24} \geq 400$ mg h/L) in adult patients treated with intermittent vancomycin. As a secondary objective we determined optimal LD size for this population based on individual PK calculations.

2. Patients and methods

2.1. Study design

A retrospective observational PK study was performed in adult patients treated with vancomycin intermittent infusion admitted to gastroenterology and nephrology departments of the General University Hospital in Prague between January and December 2016. Patients meeting the following criteria were included: age ≥18 years, not receiving dialysis, receiving vancomycin for at least 3 days, and having at least two measured vancomycin serum levels in the course of therapy. Since the study involved only analysis of routine clinical data, and at admission to the hospital the patients sign an approved general informed consent wherein they state, inter alia, that anonymous data can be used for research, study specific ethics approval was unnecessary.

2.2. Data collection

Clinical records of all evaluated patients were reviewed to collect information concerning gender, age, body weight, height, creatinine and vancomycin serum levels (sampling times included), and vancomycin dosing and administration times.

Creatinine levels were measured using Jaffe photometric method without deproteinization on Modular analyzer (Roche Diagnostics, Basel, Switzerland), while vancomycin serum concentrations were measured by a turbidimetric inhibition immunoassay (Beckman Coulter, Inc., Brea, USA).

For each patient, body mass index (BMI) and Du Bois body surface area (BSA) were estimated according to standard formulas [10].

Finally, creatinine clearance values according to the Chronic Kidney Disease Epidemiology Collaboration formula ($CrCL_{CKD\text{-}EPI}$) [11] was estimated for each patient.

2.3. Pharmacokinetic analysis

Individual PK parameters – volume of distribution (Vd), clearance (CL) and half-life (T1/2) were calculated in a two-compartmental PK model based on individual demographic, clinical data and observed vancomycin serum levels using MWPharm^{++} software (MediWare, Prague, Czech Republic). Vancomycin population PK two-compartmental model was individualized to maximize fitting of the simulated PK profile curve with observed concentration points in each patient. The fitting was performed using Bayesian estimation.

AUC_{24} on the first day of vancomycin therapy was computed using individualized PK simulations in MWPharm^{++} software.

2.4. Optimal loading dose calculation

Optimal total/normalized LD was simulated for each patient using following formulas [12]: LD (mg) = individual vancomycin Vd (L) × Cvan (mg/L), LD (mg/kg) = individual vancomycin Vd (L/kg) × Cvan (mg/L), where Cvan of 40 mg/L was set as vancomycin target peak concentration.

2.5. Statistical analysis

Descriptive parameters median, interquartile range (IQR), mean and standard deviation (SD) were calculated using MS Excel 2010 (Microsoft Corporation, Redmond, USA).

Unpaired *t*-test was used to compare AUC_{24} achieved in patients treated with and without vancomycin LD, and to compare daily maintenance doses and vancomycin PK parameters in patients treated with and without vancomycin LD.

Linear regression models were used to evaluate the relationships of vancomycin Vd with actual body weight, height, BMI and BSA, relationships of vancomycin CL with serum creatinine level and $CrCL_{CKD\text{-}EPI}$, and relationship of daily maintenance dose with $CrCL_{CKD\text{-}EPI}$ using GraphPad Prism 3.02 (GraphPad Software, Inc., La Jolla, USA).

3. Results

Forty-five patients were enrolled into the study (33 males, 12 females). Their demographic and clinical characteristics are summarized in Table 1. Vancomycin LD (1500–2500 mg; 16.0–25.9 mg/kg of body weight) was administered only in eight (17.8%) patients. Daily maintenance doses ranged between 500 and 2000 mg and significantly associated with $CrCL_{CKD\text{-}EPI}$ ($r^2 = 0.3905$; $p < 0.0001$). Mean (SD) daily maintenance dose in patients treated with and without LD were 1625 (518) and 1541 (570), respectively, and were not significantly different.

Totally 157 vancomycin serum levels for PK analysis were obtained (2–12 concentration points per patient). There were 118 concentration points taken as trough levels (sample collection 0–1 h before the next dose administration), while 39 samples were taken at expected peak level (sample collection 1–6 h after infusion completion). In 18 (40%) patients only the trough concentrations were measured, while in 27 (60%) patients were measured both trough and peak levels. Totally 71 (60.2%), 17 (14.4%) and 30 (25.4%) trough levels were in, above and below therapeutic range (10–20 mg/L), respectively. Vancomycin PK parameters in the whole study group are summarized in Table 2. Median (IQR) Vd, CL and T1/2 in patients treated with vancomycin LD were 0.65 (0.57–0.74) L/kg, 0.0373 (0.0289–0.0549) L/h/kg and 12.3 (7.5–20.2) h, respectively. The respective values in patients, who did not receive any LD were 0.70 (0.52–0.87) L/kg, 0.0277 (0.0216–0.0501) L/h/kg and 15.0 (9.3–25.8) h. Vancomycin PK parameters in the groups treated with and without LD were not significantly different.

Table 1
Demographic and clinical data.

	Median	IQR	Min	Max
Age (years)	68	60–74	24	86
Weight (kg)	80	71–100	55	133
Height (cm)	175	168–175	155	207
Body mass index (kg/m^2)	26.1	24.0–32.1	19.6	42.0
Body surface area (m^2)	1.91	1.81–2.13	1.59	2.46
Serum creatinine (μmol/L)	110	76–185	38	369
CKD-EPI creatinine clearance (mL/min)	66	36–102	12	150

Please cite this article in press as: Šíma M, et al., Importance of vancomycin loading doses in intermittent infusion regimens, J Infect Chemother (2017), https://doi.org/10.1016/j.jiac.2017.11.002